# Complete Summary

## GUIDELINE TITLE

Clinical practice guideline for the management of rheumatoid arthritis.

## BIBLIOGRAPHIC SOURCE(S)

GUIPCAR Group. Clinical practice guideline for the management of rheumatoid arthritis. Madrid: Spanish Society of Rheumatology; 2001. 170 p. [430 references]

## COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

## SCOPE

### DISEASE/CONDITION(S)

Rheumatoid arthritis

### GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

### CLINICAL SPECIALTY

Family Practice
Internal Medicine
Physical Medicine and Rehabilitation
Rheumatology

### INTENDED USERS

Physicians

## GUIDELINE OBJECTIVE(S)

- To improve the quality of care of rheumatoid arthritis (RA) in adults
- To reduce variability in the management of RA that is not dependent on patient characteristics
- To move toward the integral management of RA
- To align clinical practice more closely with the best available scientific evidence

## TARGET POPULATION

Adult patients with rheumatoid arthritis living in Spain

Note: This guideline is not intended for use in patients with juvenile rheumatoid arthritis

## INTERVENTIONS AND PRACTICES CONSIDERED

### Diagnosis

1. Use of American College of Rheumatology (ACR) criteria

### Initial evaluation

1. Clinical history and physical examination
2. Assessment of joint pain and inflammation (e.g., ACR count, 44-joint index, 28-joint index, Ritchie index)
3. Global assessment of pain by patient (e.g., Visual Analog Pain Scale, Likert scales)
4. Global assessment of disease by patient
5. Global assessment of disease by physician
6. Functional capacity assessment (use of validated questionnaires such as the Health Assessment Questionnaire [HAQ] or the Arthritis Impact Measurement Scale [AIMS])
7. Laboratory tests, including complete blood count, acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), rheumatoid factor, liver function tests, kidney function tests, and tests for presence of hepatitis B and C virus
8. Radiographic damage assessment
9. Use of composite index of disease activity (e.g., Disease Activity Score)
10. Evaluation for latent tuberculosis
11. Consideration of psychological and social factors
12. Classification of rheumatoid arthritis

### Medical treatment

1. Disease-modifying antirheumatic drugs (DMARDs) as initial treatment
    - Methotrexate (methotrexate Almirall®, Methotrexate Lederle®, Methotrexate Wassermann®, Emthexate®)

- Sulphasalazine (Salazopyrin®)
- Chloroquine (Resochin®)
- Leflunomide (Arava®)
- Injectable gold (Miocrin®)

2. Changes in treatment due to toxicity or unsatisfactory response
    - Substitution or addition of new DMARD
    - Dosage modification

    Note: Other DMARDs considered in the guideline include azathioprine (Imuran®), cyclophosphamide (Genoxal®), cyclosporin (Sandimmune®) d-penicillamine (Cuprimine® and Sufortanon®), hydroxychloroquine (Plaquenil®), oral gold (Ridaura® and Crisinor®), anti-tumor necrosis factor agents such as etanercept (Enbrel®) and infliximab (Remicade®)

3. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Ibuprofen
    - Ketoprofen
    - Naproxen
    - Diclofenac
    - Indomethacin
    - Celecoxib
    - Other NSAIDs
4. Treatment with corticosteroids
    - Prednisone
    - Methylprednisolone
    - Dexamethasone
    - Hydrocortisone
    - Betamethasone
    - Dexamethasone
    - Triamcinolone
    - Deflazacort
5. Treatment for pain
    - Analgesics (e.g., NSAIDs, acetaminophen, dipyramidole, codeine, topical capsaicin)
    - Tricyclic antidepressants
    - Anticonvulsants (e.g., gabapentin, carbamazepine)

Other treatments

1. Surgical treatment
    - Joint prosthesis
    - Synovectomy
    - Arthrodesis
2. Rehabilitative therapy
    - Thermotherapy
    - Physical exercise
    - Splints
    - Occupational therapy
3. Local therapy
    - Intra-articular steroid injection (e.g., triamcinolone hexacetonide, methylprednisolone acetate),
    - Radioisotopic synovialis

- Chemical synovialis

### Evaluation for Response

1. Use of American College of Rheumatology criteria for clinical remission
2. Use of EULAR (European League Against Rheumatism) criteria for clinical remission
3. Follow-up (based on longitudinal monitoring of parameters used in the initial evaluation)

## MAJOR OUTCOMES CONSIDERED

- Symptom relief (pain scores, stiffness, inflammation, number of swollen/tender joints)
- Joint damage (assessed radiologically)
- Disability (e.g., ability to work, use of assistive devices)
- Quality of life (e.g., scores on health assessment questionnaires, activities of daily living)
- Disease progression
- Rheumatoid arthritis functional class
- Clinical remission rate
- Changes in laboratory tests (erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor titre)
- Adverse drug effects

# METHODOLOGY

## METHODS USED TO COLLECT/SELECT EVIDENCE

### Searches of Electronic Databases

## DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search for the synthesis of the evidence on the efficacy of disease-modifying antirheumatoid drugs (DMARDs) in rheumatoid arthritis (RA) was made in four databases, for the time periods noted below:

- MEDLINE: 1966-2000
- EMBASE (Drugs and Pharmacology section): 1984-2000
- Spanish Medical Index (Indice Médico Español - IME): 1971-2000
- Cochrane Library: year 2000 version.

The articles for the bibliographic search had to meet the following inclusion criteria: 1) controlled clinical trial, meta-analysis, or systematic review; 2) study referring to one or more of the selected DMARDs; 3a) comparison of the efficacy of a drug or combined therapy vs. another drug or combined therapy including at least one of the drugs listed in Table 1 in the original guideline document, or comparison of leflunomide (LEF) or tumor necrosis factor (TNF) with placebo; 3b) if a systematic review or meta-analysis, comparison of a drug or combined therapy vs. another drug or combined therapy including at least one of the drugs listed in Table 1 of the original guideline, or with placebo; 4) study carried out in

patients with RA; 5) trial carried out in humans; and 6) published in English or Spanish.

The descriptors used were those specified in each database with regard to the research methodology (e.g., RANDOMIZED-CONTROLLED-TRIAL), rheumatoid arthritis (e.g., RHEUMATOID ARTHRITIS), and specific drugs (e.g., METHOTREXATE).

All existing systematic reviews on DMARDs were identified. Nine systematic reviews were located in the Cochrane Library that compared placebo with the following drugs: methotrexate, sulphasalazine, cyclosporin, oral gold salts, injectable gold salts, cyclophosphamide, d-penicillamine, azathioprine, and anti-malarials.

A 4-phase strategy was used to screen bibliographic records:

1. Review of the title
2. Review of the abstract
3. Request for the articles
4. Data collection and evaluation of the quality of the evidence.

Of the 287 articles requested, 162 did not meet at least one of the inclusion criteria, 13 were redundant and 9 were articles comparing drugs with placebo that had already been included in the systematic reviews of the Cochrane Library. Consequently, a total of 103 articles was included in the review, 91 of which were different clinical trials (12 were complementary articles), allowing 140 comparisons between different treatment strategies (single drugs or combinations thereof). Thus, there are 140 records in the database for the efficacy of DMARDs.

NUMBER OF SOURCE DOCUMENTS

103

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The methodological quality of the trials was assessed using the Jadad scale for rating the quality of clinical trials (below). The level of evidence was assessed in accordance with the Hadorn scale designed to evaluate the quality of the evidence of publications used to develop clinical practice guidelines (below).

Jadad Scale for Rating the Quality of Evidence from Clinical Trials

To rate the quality of a clinical trial, three questions were posed:

1. Was the study described as randomized?
2. Was the study described as double blind?

3. Was there a description of withdrawals and dropouts?

One point is given for each "yes" and 0 points for each "no". There are no intermediate scores.

An additional point is given in question 1 if the randomization method is described and is appropriate, and an additional point is given in question 2 if the method for making the study double blind is described and is appropriate.

One point is subtracted in question 1 if the randomization method is described but is inappropriate, and one point is subtracted in question 2 if the study is described as double blind, but the blinding method is inappropriate.

An article can receive a score of 0 to 5 points. An article is considered to be of good quality if the score is 3 or higher, and of poor quality if the score is less than 3.

Hadorn Scale for Rating the Quality of Scientific Evidence from Articles for Clinical Practice Guidelines (CPGs)

Level of Evidence A

1. Well-conducted multicenter randomized controlled trials including 100 or more patients
2. Well-conducted randomized trials with fewer than 100 patients, in one or more institutions
3. Well-conducted cohort studies

Level of Evidence B

4. Well-conducted case-controlled studies
5. Poorly controlled or uncontrolled studies
6. Conflicting evidence in favor of the recommendation

Level of Evidence C

7. Expert opinion

Levels 1, 2, and 3 refer to a high level of evidence (A); levels 4, 5, and 6 refer to a level of evidence with potential biases that could invalidate the results (B); and level 7 is the evidence most vulnerable to potential biases (C).

Since only clinical trials were evaluated in the synthesis of the evidence for this guideline, the levels of evidence assigned are A1 (1 on the Hadorn scale), A2 (2 on the Hadorn scale), and B (5 on the Hadorn scale).

Evaluation of the methodological quality of meta-analyses

The quality of the Cochrane Library meta-analyses was rated using the index of the quality of review articles, as revised by Oxman and Guyatt. This index is

based on answers to 10 questions about evidence quality. (See original guideline for a list of the questions.)

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

### Data Collection Form

A form was designed to collect the bibliographic data for each article, information about the study methodology, clinical data, the quality of the methodology, and the level of evidence. The first version of the form was evaluated by three reviewers (two rheumatologists and one methodologist) who applied it to 10 articles. After introducing the appropriate modifications, the reviewers began to use the form. It was necessary to change the form for later articles, however, in order to adapt it to the peculiarities of each trial (for example, the number of interventions compared, outcomes measured, and so on) and to be able to create homogeneous and unbiased evidence tables. After 13 successive versions, the definitive form was obtained, which was sufficiently valid to permit inclusion and categorization of the relevant information from each article. This form is available to interested readers (contact information is provided in the original guideline.)

### Evaluation of the Articles

Five reviewers read and evaluated the articles: two specialists in rheumatology and three in research methodology. All had been trained in techniques for the critical review of the scientific literature. Each article was read independently by two reviewers, one physician with training in epidemiology and one rheumatologist. Each reviewer completed one form for each article. Each epidemiologist-rheumatologist team then compared the individual forms and, if they agreed, completed the final form. The two reviewers discussed any discrepancies in an attempt to reach consensus. If they did not agree, the article was read and discussed by all the reviewers until agreement was reached, at which point the final form was completed.

Each form made up one record in the database designed for the synthesis of the evidence. The form describes a comparison between two different treatment interventions. This means that a trial assessing more than two treatment interventions, making different comparisons among them, would give rise to more than one form. Thus, the number of forms is larger than the number of clinical trials included in the synthesis of the evidence.

Of the 287 articles requested for review, 162 did not meet at least one of the inclusion criteria, 13 were redundant and 9 were articles comparing drugs with placebo that had already been included in the systematic reviews of the Cochrane Library. Consequently, a total of 103 articles was included in the review, 91 of which were different clinical trials (12 were complementary articles), allowing 140 comparisons between different treatment strategies (single drugs or combinations

thereof). Thus, there are 140 records in the database for the efficacy of disease-modifying antirheumatic drugs (DMARDs) (see Table 4 in the original guideline document). These 91 trials and the 140 resulting comparisons are grouped by the Jadad and Hadorn scales for classifying the quality of the evidence as shown in Tables 5 and 6 of the original guideline document, respectively.

Thirty eight of the 140 comparisons assessed a DMARD vs. certain drugs not included in the systematic review (e.g., collagen II, tiopronin, or pyrithinol). These 38 comparisons were excluded because the expert panel believed they were not relevant. Thus, the final 102 comparisons refer only to the DMARDs listed in Table 1 of the original guideline.

For the purposes of the synthesis of the evidence, the comparisons were grouped by drug to make it easier to find the clinical trials comparing a specific drug (alone or in combination) with any of the other drugs (also alone or in combination.)

For each possible comparison the guideline developers identified the number of existing studies, their level of evidence, and the intervention favored by the outcome measures collected in each study. (The tables synthesizing the outcome measures collected in each study for the comparisons are available to interested readers. Contact information is provided in the original guideline document).

The panel was consulted when a) different studies comparing the same drugs included different outcome measures, some (e.g., clinical effect) in favor of one treatment intervention and others (e.g., radiographic results) in favor of the other intervention; and b) to assess the clinical relevance of some outcome measures with statistically significant differences when the differences were not significant for many other outcomes. In these divergent cases, greater weight was given to outcome measures in agreement with the American College of Rheumatology (ACR) criteria, especially the number of swollen joints and radiographic damage. For example, a study with A2 level evidence comparing chloroquine with oral gold salts shows significant differences in favor of chloroquine with regard to strength of grip and morning stiffness; however, functional status is significantly better in the group with oral salts, and no significant differences are found between the two groups with regard to the number of swollen joints, pain, or acute phase reactants. In this case it was concluded that there were no important clinical differences in the efficacy of chloroquine and oral gold salts.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The 15 panelists formed 10 working groups of 3 persons each; thus, each panelist could serve on more than one group. The working groups were responsible for writing different chapters of the guideline. The draft recommendations made by each group were sent to the investigators, who edited and circulated them to the rest of the panelists for suggestions, and in subsequent interactions the pre-definitive version of the recommendation was written. A joint document was written based on all this information, which was submitted to all the panel

members for discussion and correction. Panelists interacted by telephone, email, regular mail, and small group meetings; the project investigators held four joint meetings with the whole panel. Thus, although each group wrote the initial version of a specific part of the guideline, all the panelists had the opportunity to contribute their knowledge and opinions in the rest of the guideline recommendations.

There was large inter-panelist variability with relation to patient classification and the treatment approach in managing rheumatoid arthritis (RA). Part of this variability may have been due to the fact that one panelist was thinking of a patient with certain characteristics while another was thinking of a patient with different characteristics. To classify patients by disease characteristics and to group them in a clinically meaningful way, various clinical variables were used. The variables considered for patient classification were: a) receipt of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids in the previous 3 months (2 categories); b) number of swollen joints (10) (3 categories); c) presence of erosions (0, 1-3 or >3 erosions) (3 categories); d) presence of elevated acute-phase reactants (2 categories); Health Assessment Questionnaire (HAQ) score (100 UI/mL) (3 categories). Combining the categories of these clinical variables yielded 144 different patient scenarios that might call for different treatment. The panelists provided anonymous and independent recommendations about the initial treatment for each of these 144 clinical scenarios.

If the recommendations differed, panelists were free to express their arguments and the evidence supporting their opinion to try to convince the rest of the panel, but they were not obliged to reach consensus. That is, this guideline is based not on consensus, but rather on the best available scientific evidence and, when this was absent or contradictory, on the judgment of an expert panel that was not forced to reach a consensus. In other words, since part of the variability in clinical practice may be due to the fact that there is insufficient scientific evidence on the efficacy of the different disease-modifying antirheumatic drugs (DMARDs), this guideline recognizes that fact and considers that it is admissible for different professionals to have different opinions.

The panel members chose the best treatment for each of the 144 different patient scenarios. Their recommendations were analyzed mathematically, especially the proportion of panelists who suggested each treatment recommendation. Since the recommended treatment was similar for many of the 144 different patient scenarios, these were grouped into 52 scenarios in which the treatment decisions were the same. Reducing the number of options seems more reasonable for guideline users, and these are the classification options reflected in the decision algorithm for the initial treatment of RA that is included at the end of this guideline. (Both the panel votes and the mathematical analysis are available to interested readers. Contact information is provided in the original guideline document).

The treatment decisions are further simplified in the text of the recommendations, where the use of corticosteroids and/or NSAIDs is treated separately from DMARD treatment, since the former are used only in particular, very specific situations. Thus, it is necessary to consider only the two objective parameters (number of swollen joints and presence of erosions) that have been shown to be the most important in disease classification due to their treatment implications.

The reduced scenario classification was used to establish the alternative treatment in case of toxicity or unsatisfactory response to initial treatment. The panelists again voted individually, and the alternative treatment options with the most votes were chosen, ordered by preference of use.

### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

### METHOD OF GUIDELINE VALIDATION

Not stated

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

These recommendations are presented in abbreviated form. Readers should refer to the text of the guideline document for a detailed discussion of each of the following topics.

Definitions for the type of evidence (1-7) and the strength and consistency of evidence grades evidence (A, B, C) are provided at the end of the Major Recommendations field.

<u>Diagnosing Rheumatic Arthritis</u>

Rheumatoid arthritis (RA) should be suspected in patients over 16 years of age who have joint inflammation or effusion of more than 6 weeks duration in three or more joints, preferably of the hands and feet. To date, the only universally accepted and used diagnostic criteria for RA are those proposed by the American College of Rheumatology (ACR) for classification of the disease.

According to the ACR, the diagnosis of RA requires confirmation of at least four of the following criteria:

1. Morning stiffness lasting at least one hour before maximal improvement, for at least 6 consecutive weeks.
2. Soft tissue swelling or effusion, observed by a physician, in at least three of the following joint areas (right or left): proximal interphalangeal (PIP),

metacarpophalangeal (MCP), wrist, elbow, knee, ankle, or metatarsophalangeal (MTP) joints, for at least 6 consecutive weeks.
3. Swelling or effusion, observed by a physician, in the proximal interphalangeal, metacarpophalangeal, or wrist joints, for at least 6 consecutive weeks.
4. Symmetrical (right and left sides) swelling or fluid in the joints mentioned in point 2, observed by a physician, for at least 6 consecutive weeks.
5. Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Demonstration of serum rheumatoid factor (RF) detected by any method that has been positive in less than 5% of control subjects.
7. Radiographic evidence in the hands or wrists of articular erosions or osteopenia in or around the affected joints.

Initial Evaluation

Patients with RA should be evaluated and treated by physicians who are familiar with the clinical management and treatment of the disease.

The initial evaluation of a patient with RA should include a clinical history and physical examination.

The clinical history should include background information that is important for RA diagnosis and treatment, including previous diseases, life style, gynecological history, and occupation. If the patient has been diagnosed with RA, the history should describe the clinical characteristics of the disease obtained by patient interview and by reviewing reports and other documents provided by the patient such as radiographs and laboratory tests. An understanding of how RA has evolved requires knowledge of all types of previous and concurrent treatments, especially with analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), including the dosage, duration, reasons for withdrawal, tolerance, and side effects.

In the physical examination, note should be taken of the presence of pain, joint inflammation, deformities, and subcutaneous nodules.

The evaluation and monitoring of RA should be based on a systematic evaluation of a minimum set of parameters including joint pain and inflammation, the patient´s global assessment of pain, global assessment of disease, functional disability, acute phase reactants, and radiologic evidence of damage.

Validated methods should be used to assess the number of painful joints and the number of swollen joints. Although the clinician will consider different factors in the choice of which index to use, this guideline recommends the ACR count.

The articular indices assess the degree of pain and swelling by counting the number of painful joints and the number of swollen joints. Different methods have been described, varying in the number of joints evaluated, although only four are in widespread use: the ACR count, Ritchie index, 44-joint index, and 28-joint index.

ACR count. The ACR count is considered to be the most complete index and is the US standard. It includes an evaluation of tenderness in 68 joints and swelling in 66 joints (excluding both hips). The following joints are assessed: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, acromioclavicular, sternoclavicular, temporomandibular, hip (only for pain), knee, ankle, subtalar, metatarsophalangeal, and proximal interphalangeal joints.

The subjective experience of pain should be assessed by the patient. It is recommended that pain be measured using a horizontal visual analog scale, 10 cm in length, divided by vertical marks into ten equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, with indicators at each end showing no pain (0) and worst pain (10).

A global assessment of disease should be made from the medical point of view and another one from the patient´s point of view. For this measurement, the use of a 10 cm horizontal visual analog scale is recommended, with vertical marks dividing it into 10 equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, indicating at each end "very good" (0) and "very poor" (10).

Global disease assessments by both the physician and the patient are useful because their evaluations may be quite different. The global assessment is very sensitive to clinical changes.

Self-perceived functional disability attributed to the disease should be evaluated using specific, previously validated questionnaires such as the Health Assessment Questionnaire (HAQ).

There are various ways to estimate functional capacity based on joint mobility or the ability to perform certain tasks as evaluated by an observer. The most widespread methods currently used consist of specific questionnaires for rheumatic disease such as the HAQ or its abbreviated form, the Modified Health Assessment Questionnaire (MHAQ), or the Arthritis Impact Measurement Scale (AIMS). They are based on the patient´s own opinion about his or her disease. These questionnaires are standardized instruments of proven validity and reliability. They evaluate those health dimensions that are most affected by RA, particularly disability, especially in relation to physical function, and pain.

This guideline recommends the use of the HAQ, a 19-item self-administered questionnaire that evaluates self-perceived physical disability to perform different activities of daily living grouped into eight areas: dressing and grooming, rising, eating, walking, hygiene, reaching, gripping, and other activities.

Laboratory tests should include the acute phase reactants (APRs) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These two APRs are good indicators of the inflammatory activity of the disease.

Laboratory tests should consist of a complete blood count, acute phase reactants (ESR, CRP), rheumatoid factor (RF), liver function (glutamic oxaloacetic

transaminase [GOT], glutamic pyruvic transaminase [GPT], gamma-glutamyl-transferase [GGT], alkaline phosphate, albumin), kidney function (creatinine), calcium, and urinalysis. The presence of hepatitis B and C virus should be evaluated (in relation to the hepatotoxicity of some of the drugs used in treatment).

These basic tests will facilitate RA monitoring and early detection of disease complications and side effects of treatment. Whether to include other, complementary tests is left to the judgment of the individual physician.

Radiographs of the hands, feet, and chest are recommended at the initial evaluation. Radiographs of the feet and hands should be repeated annually for the first 3 years of disease evolution, and thereafter as deemed appropriate.

The radiographs should be examined for the presence of bony erosions, which are more frequent at disease onset. About 70% of patients have erosions of the hands or feet by the end of the first 2 or 3 years. Their presence and the speed of onset are associated with poorer outcome. Radiographs of both hands and feet are justified by the fact that asymmetrical erosions (right or left) may appear, and by the observation that in the first 2-3 years of the disease, erosions appear only on the feet, without clinical symptoms, in up to 23-36% of patients.

A chest X-ray is recommended for initial evaluation and to identify the appearance of possible problems during the course of the disease and its treatment.

The use of a composite index of disease activity, summarizing various parameters in a single indicator, is a useful and valid procedure in assessing disease activity. As calculating such an index can be time consuming, this guideline leaves its use to the judgment of the individual rheumatologist. If one of these indices is used, however, this guideline recommends the Disease Activity Score (DAS), in any of its versions.

These indices differ in the number of parameters included as well as in the methods used for their calculation. Their advantages in comparison to conventional evaluation using single parameters are that they avoid duplicate measurements and are more sensitive to change. Their disadvantages are a certain degree of complexity in the calculations, difficulty of interpretation, and some problems related with how they are constructed.

The DAS includes the Ritchie index (see description in the original guideline document), the number of swollen joints out of 44 joints (NSJ44), ESR, and the patient´s global assessment of disease (PGA) on a visual analog scale (0 cm "very good" – 10 cm "very poor"). The DAS is calculated using the formula provided in the original guideline.

There is a modified DAS based on counts of the number of painful joints (NPJ28) and the number of swollen joints (NSJ28) out of 28 joints (refer to the original guideline document for the formula). The score for the complete DAS and the DAS28 can range from 0 to 10.

The initial and subsequent evaluation of patients with RA should include a continual estimate of disease prognosis.

The outcome of RA varies considerably among patients. Some treatment strategies, more aggressive and therefore more toxic, improve RA outcome when used early in patients with a high risk of developing functional disability or structural damage and/or of mortality. Since most radiographic changes and loss of functional capacity occur in the first few years of evolution, the earlier a disease prognosis is formulated, the earlier it will be possible to make an informed decision on the most appropriate treatment strategy.

RA outcome can be estimated more accurately by combining various factors than by considering a single factor. The factors predictive of serious disease (functional disability, radiologic erosions, and mortality) can be classified as sociodemographic, disease-dependent, and treatment-dependent. The sociodemographic factors associated with poor outcome are female sex and low educational level. Among the disease-dependent factors associated with poor outcome are positive RF, more than 20 swollen joints at disease onset, elevated CRP, ESR greater than 60 mm in the first hour, elevated HAQ at the first visit, early involvement of large joints, rapid appearance of erosions ($\geq$ 2/year), and the presence of extra-articular manifestations (rheumatoid nodules, vasculitis, scleritis, or others). The treatment factors associated with better outcome are early initiation of DMARD treatment and total time in treatment with DMARDs during the course of the disease.

Factors related with the patient´s psychological and social situation should be taken into account because they can affect the assessment of pain and development of disability.

Depression and anxiety are very frequent in RA from the time of disease onset due to the impact of confronting its diagnosis and evolution. Depression and anxiety are closely related with chronic pain and the development of disability. Some psychological characteristics of the patient (level of perceived helplessness, coping ability, level of self-management) play an important role as factors predictive of disability and health status. Patients who receive social support from family members, especially from spouses, have better outcomes and less disability.

A detailed evaluation should be made to rule out latent tuberculosis infection before beginning treatment with immunosuppressants, anti-tumor necrosis factor (TNF) agents, or corticosteroids. If latent tuberculosis infection is present, prophylactic treatment with isoniazide is recommended.

Classifying Rheumatic Arthritis

The classification of RA is based on the two characteristics that have the most influence on treatment decisions and outcome: the presence or absence of erosions and the number of swollen joints. This classification may be made more precise if other factors such as APR, HAQ, and RF are taken into account.

RA cannot be neatly classified into different categories. In this guideline, the classification of patients is based on two principles: first, classifying RA is useful for making treatment decisions and estimating patient outcome; second, the classification should help the physician in actual practice. In accordance with these two principles, RA is classified based on the two parameters that, in the panel´s opinion, have the most influence on treatment decision and outcome: the presence of erosions and the number of swollen joints. The use of two categories for the presence of erosions (yes/no) and two categories for the number of swollen joints (<6/≥6), gives four types of RA. Further differentiation in the classification process by considering other factors such as APRs, HAQ, and RF results in 144 different patient types, from the most mild clinical presentation (no erosions, <6 swollen joints, normal APRs, HAQ<1, and negative RF) to the most severe (erosions present, >10 swollen joints, elevated APRs, HAQ≥1, and high titers of positive RF). Each patient, according to the initial disease characteristics, should begin a specific treatment option (see chapter 4 of the original guideline document).

Two types of RA are excluded from this classification: "burnt-out" or end-stage RA and pseudopolymyalgic RA.

"Burnt-out" or end-stage RA is RA without inflammatory activity and with complete or practically complete destruction of the patient´s joints. It is characterized clinically by joint pain at rest or with minimal exertion, joint deformities, severe muscular atrophy, extreme functional disability, and radiographic evidence of major joint destruction (erosions, subluxations, and ankylosis). The evaluation should rule out the presence of the extra-articular complications or manifestations of RA that most frequently appear at this stage of the disease, for example, skin ulcers, vasculitis, or amyloidosis.

Pseudopolymyalgic RA is a disease that affects patients over 60 years of age and is characterized by the sudden onset of symptoms, mainly affecting the proximal joints (shoulders and hips) as well as the knees and carpal joints. It is accompanied by considerable morning stiffness, negative RF, and a marked increase in APRs. Erosions do not usually develop and the prognosis is generally good, with possible spontaneous remission of the disease in 6-24 months.

The differential diagnosis of pseudopolymyalgic RA is difficult since it is very similar to polymyalgia rheumatica. It is usually managed effectively with corticosteroids. If a satisfactory response is not obtained, it should be treated the same as RA, taking special considerations into account for elderly patients.

## Medical Treatment of Rheumatoid Arthritis

### Initial treatment of rheumatoid arthritis

In general, patients with RA should be treated with a DMARD as soon as the disease is diagnosed.

An attempt may be made to treat only with NSAIDs and/or corticosteroids for a maximum of 3 months, and only in patients who have not used these drugs during the 3 months before the disease was

diagnosed, who have fewer than 6 swollen joints, no erosions, negative RF, and normal APRs.

All RA patients who remain symptomatic (with pain and swelling) despite treatment with DMARDs should be treated with steroidal or nonsteroidal anti-inflammatory agents and analgesics.

Because of its efficacy and toxicity profile, methotrexate is the recommended initial treatment in all patients who have not previously received DMARD treatment. Nevertheless, initial treatment with other drugs is also considered acceptable, in accordance with the clinical classification of disease shown in the accompanying table.

Simplified Clinical Classification of RA

| SIMPLIFIED CLINICAL CLASSIFICATION OF RA | | Recommended initial treatment, by order of preference (supporting evidence) |
|---|---|---|
| No erosions | <6 swollen joints | Methotrexate (1)<br>Sulphasalazine (2)<br>Chloroquine (3) |
| | ≥6 swollen joints | Methotrexate (1)<br>Injectable gold (4) |
| Erosions present | <6 swollen joints | Methotrexate (1) |
| | ≥6 swollen joints | Methotrexate (1)<br>Leflunomide (5)<br>Methotrexate + injectable gold (6) |

(1) Methotrexate is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences have been found in the efficacy of methotrexate compared with etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).

(2) Sulphasalazine is more efficacious than hydroxychloroquine (A2 evidence), and no significant differences have been found in the efficacy of sulphasalazine compared with leflunomide, methotrexate (A1 evidence), oral or injectable gold, and D-penicillamine (B evidence).

(3) Chloroquine is not significantly different in efficacy from cyclosporin, oral gold (A2 evidence), azathioprine, injectable gold, and D-penicillamine (B evidence).

(4) Injectable gold is not significantly different in efficacy from oral gold (A1 evidence), cyclosporin and methotrexate (A2 evidence), or chloroquine, D-

penicillamine and sulphasalazine (B evidence). It is less efficacious than azathioprine and cyclophosphamide (B evidence).

(5) Leflunomide (A1 evidence) shows no differences in efficacy as compared to methotrexate and sulphasalazine (A1 evidence).

(6) No clinical trials have evaluated the efficacy of treatment with methotrexate+injectable gold (C evidence).

Changes in treatment

Treatment failure or toxicity should be evaluated within a maximum of 3 months, and a change in treatment should be considered.

Whatever initial treatment is chosen, the patient should be closely monitored. If a satisfactory response is not obtained in 3 months or if serious drug-related toxicity develops, the treatment should be modified.

Changes in treatment due to toxicity or unsatisfactory response

If serious adverse effects appear, an alternative treatment should be substituted for the treatment of first choice. If the treatment shows no toxicity but the response is unsatisfactory even after using the maximum dose, an alternative treatment should be substituted for the treatment of first choice.

For patients in whom alternative treatments fail due to unsatisfactory response, toxicity, or other reasons, the use of any DMARD or DMARD combination of proven efficacy is recommended (see tables 4, 5 and 8 of the original guideline document); if these fail, experimental treatments may be tried.

Changes in treatment due to toxicity or unsatisfactory response should be made in accordance with the following tables.

Alternative treatment in case of severe toxicity of initial treatment

| SIMPLIFIED CLINICAL CLASSIFICATION OF RA | | First-choice treatment used | Alternative treatment in case of toxicity, in order of preference (supporting evidence) |
|---|---|---|---|
| No erosions | <6 swollen joints | Methotrexate | Leflunomide (1)<br>Injectable gold (2)<br>Sulphasalazine (4) |
| | | Sulphasalazine | Methotrexate (3)<br>Injectable gold (2) |

| SIMPLIFIED CLINICAL CLASSIFICATION OF RA | | First-choice treatment used | Alternative treatment in case of toxicity, in order of preference (supporting evidence) |
|---|---|---|---|
| | | Chloroquine | Methotrexate (3)<br>Injectable gold (2) |
| | ≥6 swollen joints | Methotrexate | Leflunomide (1)<br>Injectable gold (2) |
| | | Injectable gold | Methotrexate (3)<br>Leflunomide (1) |
| Erosions present | <6 swollen joints | Methotrexate | Leflunomide (1)<br>Injectable gold (2)<br>Sulphasalazine (4) |
| | ≥6 swollen joints | Methotrexate | Leflunomide (1)<br>Injectable gold (2)<br>Sulphasalazine (4) |
| | | Leflunomide | Methotrexate (3)<br>Anti-TNF (5) |
| | | Methotrexate+injectable gold | Leflunomide (1)<br>Anti-TNF (5) |

(1) Leflunomide (A1 evidence) shows no differences in efficacy as compared to methotrexate and sulphasalazine (A1 evidence).

(2) Injectable gold has not been shown to have significant differences in efficacy as compared to oral gold (A1 evidence), cyclosporin and methotrexate (A2 evidence), or chloroquine, D-penicillamine and sulphasalazine (B evidence). It is less efficacious than azathioprine and cyclophosphamide (B evidence).

(3) Methotrexate is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences in the efficacy of methotrexate have been found in comparison with etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).

(4) Sulphasalazine is more efficacious than hydroxychloroquine (A2 evidence) and no significant differences have been found in the efficacy of sulphasalazine compared with leflunomide, methotrexate (A1 evidence), oral or injectable gold, and D-penicillamine (B evidence).

(5) Anti-TNF agents (infliximab and etanercept) have been shown to be efficacious in the treatment of RA (A1 evidence), and they show no significant

differences in efficacy with respect to methotrexate (B evidence for infliximab and A1 for etanercept).

Alternative treatment in case of unsatisfactory response to initial treatment

| SIMPLIFIED CLINICAL CLASSIFICATION OF RA | | First-choice treatment used | Alternative treatment in case of unsatisfactory response, in order of preference (supporting evidence) |
|---|---|---|---|
| No erosions | <6 swollen joints | Methotrexate | Leflunomide (1) |
| | | Sulphasalazine | Methotrexate (2)<br>Leflunomide (1) |
| | | Chloroquine | Methotrexate (2)<br>Leflunomide (1) |
| | ≥6 swollen joints | Methotrexate | Leflunomide (1) |
| | | Injectable gold | Methotrexate (2)<br>Leflunomide (1) |
| Erosions present | <6 swollen joints | Methotrexate | Leflunomide (1) |
| | ≥6 swollen joints | Methotrexate | Leflunomide (1)<br>Anti-TNF agents (3)<br>Methotrexate + anti-TNF (4)<br>Methotrexate + chloroquine + sulphasalazine (5) |
| | | Leflunomide | Methotrexate (2)<br>Anti-TNF agents (3)<br>Methotrexate + anti-TNF (4) |
| | | Methotrexate+injectable gold | Leflunomide (1)<br>Anti-TNF (3) |

(1) Leflunomide (A1 evidence) has not shown differences in efficacy compared with methotrexate and sulphasalazine (A1 evidence).

(2) Methotrexate is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences in efficacy have been found in methotrexate as compared to etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).

(3) Anti-TNF agents (infliximab and etanercept) have been shown to be efficacious in the treatment of RA (A1 evidence) in comparison with placebo, and they show no significant differences in efficacy as compared to methotrexate (B evidence for infliximab and A1 for etanercept).

(4) The combination of methotrexate+anti-TNF agents (infliximab or etanercept) has been shown to be more efficacious than methotrexate alone (B evidence).

(5) The combination of methotrexate+chloroquine+sulphasalazine has been shown to be more efficacious than methotrexate alone or chloroquine+sulphasalazine (A2 evidence).

In addition to the panel´s recommendations, there is scientific evidence regarding the efficacy of several drug combinations in case of failure of treatment with methotrexate or the antimalarials.

In case of failure with methotrexate, the following combinations have been shown to be more efficacious:

Methotrexate+cyclosporin (A1 evidence)
Methotrexate+chloroquine (A2 evidence)
Methotrexate+azathioprine (B evidence)

In case of failure with the antimalarials, the following combinations have been shown to be more efficacious:

Sulphasalazine+hydroxychloroquine (A2 evidence)
Methotrexate+hydroxychloroquine (B evidence)

Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs are used to modify the symptoms of RA. The use of NSAIDs is recommended at disease onset, when a new DMARD is introduced, and when uncontrolled isolated symptoms persist despite good response to a DMARD.

The use of NSAIDs is recommended in the following cases: 1) At disease onset, if it is low risk (<6 swollen joints, no erosions, negative RF, and normal APRs), they can be used alone or in combination with corticosteroids for no longer than 3 months; 2) when a new DMARD is introduced, NSAIDs can be used until the DMARD is capable of controlling the disease and its symptoms, generally from 2 to 12 weeks depending on the time needed for the DMARD to reach effective therapeutic levels; and 3) when uncontrolled symptoms persist (painful inflammation or swelling or morning stiffness) despite DMARD treatment, and there is no evidence of inflammatory activity that would justify raising the DMARD

dosage or changing to a new treatment. The need for gastric protectors should be evaluated in each patient.

Treatment with corticosteroids

The use of oral corticosteroids at low doses is recommended in patients in whom NSAIDs are not effective or are contraindicated for any reason. They can be used instead of NSAIDs or in association with them.

The corticosteroids should not replace treatment with DMARDs unless their possible role as a disease modifying agent should be shown. They are indicated as the treatment of choice only in the case of pseudopolymyalgic RA.

Corticosteroids should be used: 1) when NSAIDs are contraindicated or have a high risk of adverse effects (the elderly, associated morbidity); 2) as bridge therapy until the onset of DMARD action; 3) when NSAIDs do not effectively control inflammation (generally, by adding corticosteroids to the NSAID treatment); and 4) in the treatment of pseudopolymyalgic RA.

Treatment for pain

Analgesics are indicated to control pain. If there is no response, surgical treatment can be considered, especially to restore function and mobility.

Pain-control treatment should be instituted if pain persists despite the adoption of previous disease-control measures. Simple analgesics (e.g., acetaminophen, acetylsalicylic acid [ASA]) should be used first. If pain persists, dipyridamole, NSAIDs, or codeine may be used.

If pain is due to neuropathy, tricyclic antidepressants (amitryptiline) and some anticonvulsants (gabapentin or carbamazepine) may be used. When pain is very localized, local analgesics such as capsaicin cream may be used.

Surgical treatment should be considered when pain does not respond to pharmacological treatments and is due to joint destruction, producing changes in the patient´s functional capacity. If pain is intense, there is no response to previous analgesic treatments, and surgery is not an option, opiate analgesics may be administered.

Special considerations in the treatment of elderly patients

Kidney and liver function should be monitored in elderly patients, and the dosage intervals of the drugs eliminated by these routes should be adapted accordingly.

The dosage of drugs eliminated by the renal route should be adjusted in elderly patients. This is because: 1) Even in the absence of kidney disease, renal clearance in elderly individuals is decreased by 35-50%, and 2) The elderly, and especially those who suffer RA, have reduced muscular mass, which produces a decline in the production of creatinine. Thus, an elderly individual may have a normal creatinine value even though creatinine clearance is altered.

Aging may also alter hepatic function, thus the metabolization of drugs that are broken down in the liver may also be reduced.

The possible appearance of adverse effects and drug interactions should be monitored in elderly patients.

In general, elderly patients have more than one disease and need treatment with multiple drugs. This, together with the higher frequency of adverse reactions in the elderly, means there is an increased probability of drug interactions and contributes to a larger number of side effects.

Special considerations in the treatment of rheumatoid arthritis during pregnancy

Women of childbearing age should be informed of the possible effects of RA and its treatment on pregnancy.

There is no evidence that RA has a negative effect on pregnancy outcome. The symptoms of RA disappear during pregnancy in 70% of cases, to reappear early in the postpartum period. Nevertheless, the disease commonly fluctuates and, at the very least, cycles of analgesics will be required.

The use of NSAIDs during pregnancy and breastfeeding should be avoided insofar as possible. Corticosteroids can be used under controlled conditions. DMARDs should be managed on an individual basis, and should preferably be continued during pregnancy.

NSAIDs should be avoided in the first and last trimester and during breastfeeding. If necessary, NSAIDs with a short half-life (ibuprofen or ketoprofen) should be used.

There is no evidence that the corticosteroids produce serious adverse effects at average doses during pregnancy, except for promoting glucose intolerance, fluid retention, and hypertension. Consequently, they should be administered under controlled conditions.

With regard to the use of DMARDs during pregnancy and breastfeeding, in the case of aggressive disease, the DMARD should be maintained at the minimum effective dosage, unless it has been shown to affect the embryo, fetus, or infant.

Criteria for Response to Treatment

The objective of RA treatment is to induce complete disease remission or, alternatively, to achieve the best possible response.

RA patients who have spontaneous or drug-induced remissions in the course of their disease have a better medium-term outcome than those who have persistent clinical activity. However, the rates of complete remission with DMARDs and/or corticosteroids are low (18-25%) and are rarely prolonged. Complete disease remission, or at least attainment of the lowest possible level of inflammatory activity, is the only way to improve disease outcome.

Two basic approaches to defining clinical remission in RA have been described: the ACR criteria and the EULAR (European League Against Rheumatism) criteria.

ACR criteria for clinical remission

- Morning stiffness absent or not exceeding 15 minutes
- No fatigue
- No joint pain (by clinical history)
- No joint tenderness
- No soft tissue swelling in joints or tendon sheaths
- Normal erythrocyte sedimentation rate.

The presence of five or more of these criteria for at least 2 months is sufficient to classify a patient as in complete remission. Among the disadvantages of these criteria are the lack of guidelines on how to measure them, the fact that they are dichotomous, and that two of the criteria (fatigue and morning stiffness) are not included in the parameters recommended for the evaluation of RA patients.

EULAR criteria for clinical remission

The EULAR criteria use the DAS as a continuous variable of disease activity. A cut-off point below 1.6 on the DAS corresponds to the ACR definition of remission. Since the measurement scale is continuous, the cut-off point recommended by the EULAR may vary depending on future investigations.

Patients with RA should be clinically monitored for an indefinite period of time. Patients in complete disease remission should be seen every 6 months or 1 year, and patients with recent disease onset, frequent flare-ups, or persistent activity should be seen "on demand" (in general, every 1 or 2 months), depending on the treatment used and disease activity, until control is achieved.

To avoid an overload of patients, they can be seen in primary care during the periods between rheumatologist appointments to ensure clinical and laboratory monitoring and permit rapid referral to the specialist in case of disease reactivation and/or adverse effects.

Follow-up of patients with RA should be based on longitudinal monitoring of the parameters described in the initial evaluation: joint pain and inflammation, global pain assessment by the patient, global assessment of disease activity, functional disability, acute phase reactants, and radiologic damage.

One way to improve the quality of care for patients is to apply the treatment response criteria designed for use in clinical trials to daily clinical practice. Thus, it is proposed that the same parameters assessed at the initial evaluation be used to monitor patients and evaluate their response to treatment: pain and joint inflammation, global pain assessed by the patient, global disease activity assessed by the patient and by the physician, functional disability, and acute phase reactants. The same instruments used in the initial evaluation should be used in follow-up.

The physician´s subjective assessment of disease activity, although it is the most commonly used criterion in daily practice, is not recommended as the only criterion for response to treatment.

The treatment response criteria applied to individual patients should take into account: a) changes in disease activity and b) current level of activity. The clinician should evaluate the response to treatment, classifying it as satisfactory (complete remission of disease or sufficient even if not complete remission) or unsatisfactory (complete or almost complete lack of improvement). The evaluation can be made in accordance with any of the response criteria proposed in sections 5.4.1, 5.4.2, 5.4.3, and 5.4.4 of the original guideline document.

There is no published clinical experience in daily practice with any of the response indices developed for clinical trials. This guideline proposes the use of treatment response criteria based on two categories: satisfactory response, meaning complete remission of disease or a "sufficient" response, even though complete remission is not achieved, and unsatisfactory response, meaning complete or almost complete lack of improvement. The clinician can apply different response criteria to arrive at each of these categories. Two approaches that have been tested are described below: the ACR criteria for improvement and the EULAR definition of response. Other measures, such as the simplified Scott index and the Paulus criteria, are described in the guideline.

ACR response criteria

The ACR response criteria define a dichotomous result (response/no response) according to the following criteria:

- At least 20% improvement in the painful joint count and in the swollen joint count; and
- At least 20% improvement in at least three of the following parameters: ESR or APR, physician´s global assessment of disease activity, patient´s global assessment of disease activity, patient´s assessment of pain, and physical disability.

These criteria are known as the ACR20, reflecting the need for a 20% improvement in each parameter, which is considered the clinically relevant cut-off point. The fact that the criteria do not consider the current activity level limits its application in daily clinical practice unless it is adapted to take this factor into account. Thus it is proposed that these criteria be applied with the following modification:

- Satisfactory response: Meeting the following three criteria: 1) ACR20; 2) fewer than 6 swollen joints; and 3) no impairment of any joint producing intolerable loss of functional capacity in the opinion of the patient or physician.
- Unsatisfactory response: Not meeting the criteria for satisfactory response.

EULAR response criteria

The EULAR criteria use the disease activity scale (DAS), which takes into account both the degree of improvement and the patient´s current situation. It has been shown to be comparable in validity to the ACR response criteria in clinical trials. The definitions of satisfactory and unsatisfactory response, in accordance with the original DAS and DAS28, are shown in the original guideline document.

Surgical Treatment

The rheumatologist should consider surgical treatment in any of the following situations: 1) when articular function does not improve or is notably worse; 2) when incapacitating pain persists; or 3) when there are potentially serious or limiting neurological complications.

The joint prosthesis is the most efficient surgical means to arrest progressive loss of functional capacity. Synovectomy may produce slight improvement in the synovectomized joints, but this effect is not maintained at 3 years. Arthrodesis is a good control measure but is more limited from the functional point of view.

Appropriate medical treatment will reduce the indications for surgery and will improve the likelihood of surgical success. Consultation with an orthopedic surgeon should not always be an indication for surgery, but the exchange of opinions and clinical evaluation will help improve the patient´s clinical and functional status.

Before surgical intervention, an evaluation should be made of bone quality, the patient´s motivation and preferences, an estimate of how surgery would change the course of the disease, and the extent to which it can reconstruct articular function and make the patient more independent.

Rehabilitation Therapy

The objective of a rehabilitation program in RA patients is to improve pain, joint mobility, and performance of the activities of daily living. This is intended to prevent disability and maintain maximum personal independence. Rehabilitative techniques that can be used in treating RA patients are thermotherapy, physical exercise, prescription of splints, and occupational therapy.

Patients who undergo a rehabilitation program have 25 to 40% improvement in function.

Local Therapy

Local therapy in RA is indicated in joints with persistent disease activity despite adequate systemic control of the disease. The smaller the radiographic damage in a joint and the less systemic inflammatory activity of RA, the higher the probability that local treatment will have good results. Intra-articular infiltration with corticosteroids is the procedure of choice. Other procedures are radioisotopic synoviolisis and chemical synoviolisis.

## Extra-articular Complications of Rheumatoid Arthritis

### Amyloidosis

Secondary amyloidosis should be suspected in RA patients who develop proteinuria, renal failure, gastrointestinal symptoms, myocardiopathy and/or hepatomegaly, and in those having elevated phase reactants concurrent with little clinical activity.

### Anemia

Anemia in RA is usually asymptomatic, therefore periodic blood cell counts should be obtained including erythrocyte, leukocyte and platelet counts, calculation of the mean corpuscular volume (MCV), reticulocyte count, and general liver and kidney function tests.

### Cardiological complications

Cardiac involvement should be suspected in the presence of pericardial-type pain, heart failure, or conduction abnormalities. The two most frequent complications are pericarditis and myocarditis.

### Osteoporosis

Osteoporosis should be suspected in the presence of vertebral or peripheral fractures not due to trauma. When RA is first diagnosed, all patients should be evaluated for the main risk factors for fracture and loss of bone mass; this analysis should include both RA-associated and independent risk factors.

### Pulmonary complications

The presence of pleuritic pain, dyspnea, or hemoptysis is suggestive of pulmonary disease in RA patients. Pulmonary complications may include pleural disease, rheumatoid nodules, interstitial fibrosis, or bronchiolitis obliterans with organizing pneumonia.

### Felty´s syndrome

Felty´s syndrome is indicated by the presence of splenomegaly, leukopenia (< 3,500/$mm^3$), and neutropenia (<2,000/$mm^3$) in patients meeting RA criteria.

### Secondary Sjögren´s syndrome

A patient with RA is considered to have secondary Sjögren´s syndrome (SSS) if there are signs and symptoms indicative of xerophthalmia and xerostomia.

### Vasculitis

Rheumatoid vasculitis is understood to be a set of vascular processes (periungual splinter hemorrhages, palpable purpura, polyarteritis nodosa) with variable outcome and treatment.

Definitions

Hadorn Scale for Rating the Quality of Scientific Evidence from Articles for Clinical Practice Guidelines (CPGs)

Level of Evidence A

1. Well-conducted multicenter randomized controlled trials including 100 or more patients
2. Well-conducted randomized trials with fewer than 100 patients, in one or more institutions
3. Well-conducted cohort studies

Level of Evidence B

4. Well-conducted case-controlled studies
5. Poorly controlled or uncontrolled studies
6. Conflicting evidence in favor of the recommendation

Level of Evidence C

7. Expert opinion

Levels 1, 2, and 3 refer to a high level of evidence (A); levels 4, 5, and 6 refer to a level of evidence with potential biases that could invalidate the results (B); and level 7 is the evidence most vulnerable to potential biases (C).

Since only clinical trials were evaluated in the synthesis of the evidence on DMARD treatment for this guideline, the levels of evidence assigned are A1 (1 on the Hadorn scale), A2 (2 on the Hadorn scale), and B (5 on the Hadorn scale).

## CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for the Diagnosis and Treatment of a Patient with Rheumatoid Arthritis:

- Branch 1: Patients with fewer than 6 swollen joints
- Branch1-1: Patients with fewer than 6 swollen joints, no erosions, not treated with NSAIDs and/or corticosteroids for at least 3 months
- Branch 2: Patients with 6 to 10 swollen joints
- Branch 3: Patients with more than 10 swollen joints, erosions present
- Branch 3-1: Patients with more than 10 swollen joints, no erosions

# EVIDENCE SUPPORTING THE RECOMMENDATIONS

## TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The systematic scientific review of the literature on disease-modifying antirheumatic drugs (DMARDs) made it possible to identify the level of evidence supporting the panel recommendations for medical treatment. For other recommendations, each panelist or group provided the evidence on which they had based their recommendations. In other words, support for the recommendations based on a systematic review and evaluation of the scientific evidence in this guideline is limited to management with DMARDs (see "Major Recommendations"). The rest of the recommendations are based on a non-systematic review of the scientific evidence, which is cited as the bibliographic reference, or on expert opinion.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Treatment of rheumatoid arthritis might:

- Provide symptom relief (pain, stiffness, inflammation)
- Reduce joint damage
- Decrease disability
- Maintain or improve quality of life
- Slow disease progression

### POTENTIAL HARMS

The major potential toxicity associated with pharmacologic treatment of rheumatoid arthritis is as follows:

- Antimalarials -- gastrointestinal, retina, skin
- Anti-Tumor Necrosis Factor (Anti-TNF) agents -- hematologic, central nervous system, immune system (toxicity assumed)
- Azathioprine -- hematologic, gastrointestinal
- Cyclophosphamide -- gonadal, urological, bone marrow
- Cyclosporin A -- kidney, hypertension
- D-penicillamine -- skin, gastrointestinal, kidney
- Leflunomide -- pulmonary, gastrointestinal, hepatic
- Methotrexate -- pulmonary, hepatic, hematologic, gastrointestinal, and neurological
- Gold salts -- hematologic and renal
- Sulphasalazine -- central nervous system, gastrointestinal, hematologic
- Refer to Chapter 6 in the original guideline document for additional information on side effects associated with each type of pharmacologic treatment.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

Contraindications to Use of Antimalarials

- Allergy to 4-aminoquinoline derivatives
- Retinopathy or visual field deterioration

Contraindications to Use of Anti-Tumor Necrosis Factor (Anti-TNF) Agents

- Sepsis or clinically manifest infections and/or abscesses
- Past medical history of hypersensitivity to infliximab or other murine proteins

Contraindications to Use of Azathioprine

- Known neoplastic disease

Contraindications to Use of Cyclophosphamide

- Pregnancy
- Chronic or active infection
- Liver disease
- History of neoplasia
- Renal failure is a relative contraindication that requires adjustment of dosage.

Contraindications to Use of Cyclosporin A

- Coexisting cancer (except non-melanoma skin cancer)
- Uncontrolled hypertension
- Renal dysfunction
- Uncontrolled infections
- Primary and secondary immunodeficiency

Contraindications to Use of D-penicillamine

- Kidney disease
- Blood disorders (e.g., leukopenia, thrombocytopenia)

Contraindications to Use of Leflunomide

- Serious immunodeficiency
- Dysplasias
- Uncontrolled infection (due to the theoretical possibility of immunosuppression)
- Moderate or severe renal failure (there is no experience in this group of patients)
- Liver function disorder
- Significant bone marrow disorder
- Severe hypoproteinemia

Contraindications to Use of Methotrexate

Absolute contraindications

- Pregnancy
- Alcohol abuse

- Hepatitis B or C
- Cirrhosis of any origin

Relative contraindications

- Renal failure
- Chronic pulmonary disease
- Active infection not associated with Felty´s syndrome

Contraindications for Use of Gold Salts

- Severe liver or kidney disease
- Blood and marrow disorders

Contraindications for Use of Sulphasalazine

- Allergy to salicylates or sulfonamides

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

The recommendations on treatment with Disease-modifying antirheumatic drugs (DMARDs) were based on a literature review and synthesis of the evidence; all other recommendations were based on a non-systematic literature review and/or the work of an expert panel.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

GUIPCAR Group. Clinical practice guideline for the management of rheumatoid arthritis. Madrid: Spanish Society of Rheumatology; 2001. 170 p. [430 references]

## ADAPTATION

Not applicable: The guideline was not adapted from another source.

## DATE RELEASED

2001

## GUIDELINE DEVELOPER(S)

Advanced Research Techniques in the Health Services - Private For Profit Research Organization
Spanish Society of Rheumatology - Medical Specialty Society

## GUIDELINE DEVELOPER COMMENT

This guideline was an initiative of the Spanish Society of Rheumatology. The following institutions collaborated in carrying out this initiative:

Spanish Society of Rheumatology (Sociedad Española de Reumatología - SER). The SER promoted the idea for this guideline, chose the research group to develop it, helped select the panel of experts, sponsored its development, and presented the project to the financing organization.

Health Services Research Unit (Unidad de Investigación en Servicios de Salud - UISS). When the SER decided to produce the guideline in late 1998, the Society proposed that it be developed by the UISS. At that time the UISS was a research unit within the Carlos III Health Institute (ISCIII). The UISS began to develop the guideline, but organizational changes in the ISCIII took place at the end of 2000. The UISS then became a private company with the name of TAISS, part of whose research staff came from the UISS.

Ignacio de Mercado Foundation (Fundación Ignacio de Mercado - FIdeM) for research and education in the health services. The FIdeM contracted project personnel who were not on the staff of the UISS.

Advanced Research Techniques in the Health Services (Técnicas Avanzadas de Investigación en Servicios de Salud, S.L. - TAISS). TAISS is a company devoted to producing knowledge to improve decision making in the health sector at the macro (policy) level, as well as at the meso (management) and micro (physician-patient) levels. Its research staff came from the UISS. All the investigators who participated in the project at its inception have continued to work on it.

Novartis. Novartis is the organization that financed the development of this guideline. It also oversaw each project activity and, together with the SER, monitored project tasks to ensure they were carried out in a correct and timely fashion.

## SOURCE(S) OF FUNDING

Novartis financed the development of the original, Spanish-language version of this guideline: Guía de Práctica Clínica para el Manejo de Artritis Reumatoide en España.

The English-language version of the guideline was made possible thanks to Abbott Laboratories, which provided financing for the translation.

## GUIDELINE COMMITTEE

Clinical Practice Guideline for the Management of Rheumatoid Arthritis in Spain. Spanish Society of Rheumatology (GUIPCAR) Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Each of the panelists who contributed to the formulation of these guidelines signed a document assuring that he or she was not affected by any of the conflicts described in a comprehensive list of possible conflicts of interest. Nominees with conflicts of interest were excluded.

## GUIDELINE STATUS

This is the current release of the guideline.

A revision is planned for 2004.

## GUIDELINE AVAILABILITY

Electronic copies (English): Available from the Spanish Society of Rheumatology Web site:

- HTML
- Portable Document Format (PDF)
- ASCII Text

Print copies (Spanish): Available from the Spanish Society of Rheumatology. C/Recoletos 9 – 1st floor, 28001 Madrid, Spain; Telephone: +34 91 5767799; Fax: +34 91 5781133; e-mail: ser@ser.es.

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Clinical Practice Guideline for the Management of Rheumatoid Arthritis. Quick Reference Guide. Madrid: Spanish Society of Rheumatology; 2001. 18 p. Electronic copies: Available from the Spanish Society of Rheumatology Web site:
    - HTML
    - Portable Document Format (PDF)
    - ASCII Text

Print copies (Spanish): Available from the Spanish Society of Rheumatology. C/Recoletos 9 – 1st floor, 28001 Madrid, Spain; Telephone: +34 91 5767799; Fax: +34 91 5781133; e-mail: ser@ser.es.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on June 12, 2003. The information was verified by the guideline developer on June 24, 2003.

## COPYRIGHT STATEMENT

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